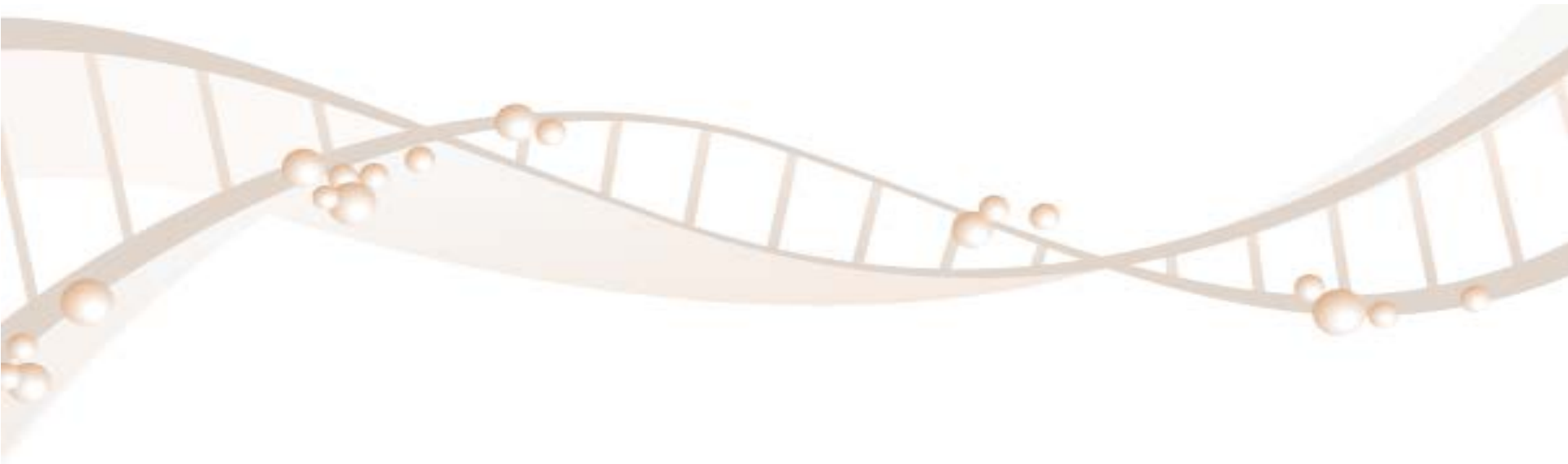
ISIS PHARMACEUTICALS

Investor Presentation

May 7, 2013



Forward Looking Language Statement

This presentation includes forward-looking statements regarding Isis Pharmaceuticals' business, Isis' financial position and outlook, and the therapeutic and commercial potential of Isis' technologies and products in development, and the contemplated offering of common stock and the anticipated use of proceeds therefrom. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO and the contemplated offering of common stock and the anticipated use of proceeds therefrom, is a forward-looking statement and are made pursuant to the Safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2012 and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

Isis claims the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

Isis Pharmaceuticals, Inc. has filed a registration statement and a prospectus supplement with the SEC for the offering to which this communication relates. Before you invest, you should read the prospectus in that registration statement, the prospectus supplement and other documents Isis Pharmaceuticals, Inc. has filed with the SEC for more complete information about Isis Pharmaceuticals, Inc. and this offering. You may get these documents for free by visiting EDGAR on the SEC Website at www.sec.gov. Alternatively, any underwriter or other dealer participating in the offering will arrange to send you the prospectus and prospectus supplement if you request them ay calling Goldman, Sachs & Co. at 1- 866-471-2526 or J.P. Morgan at 1-866-803-9204.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

Common Stock Offering

Securities Description	Common Stock
Ticker / Listing	ISIS / NASDAQ
Type of Shares	100% Primary
Offering Size	9 million shares
Over Allotment Option	15%
Anticipated Pricing Date	Wednesday, May 8, 2013, after Close
Lock Up	90 days (Company, Board of Directors, and Officers)
Use of Proceeds	Research and development and general corporate purposes
Underwriters	Goldman, Sachs & Co., J.P. Morgan
Lead Manager	Stifel
Co-managers	BMO Capital Markets; Cowen and Company, LLC; Needham & Company

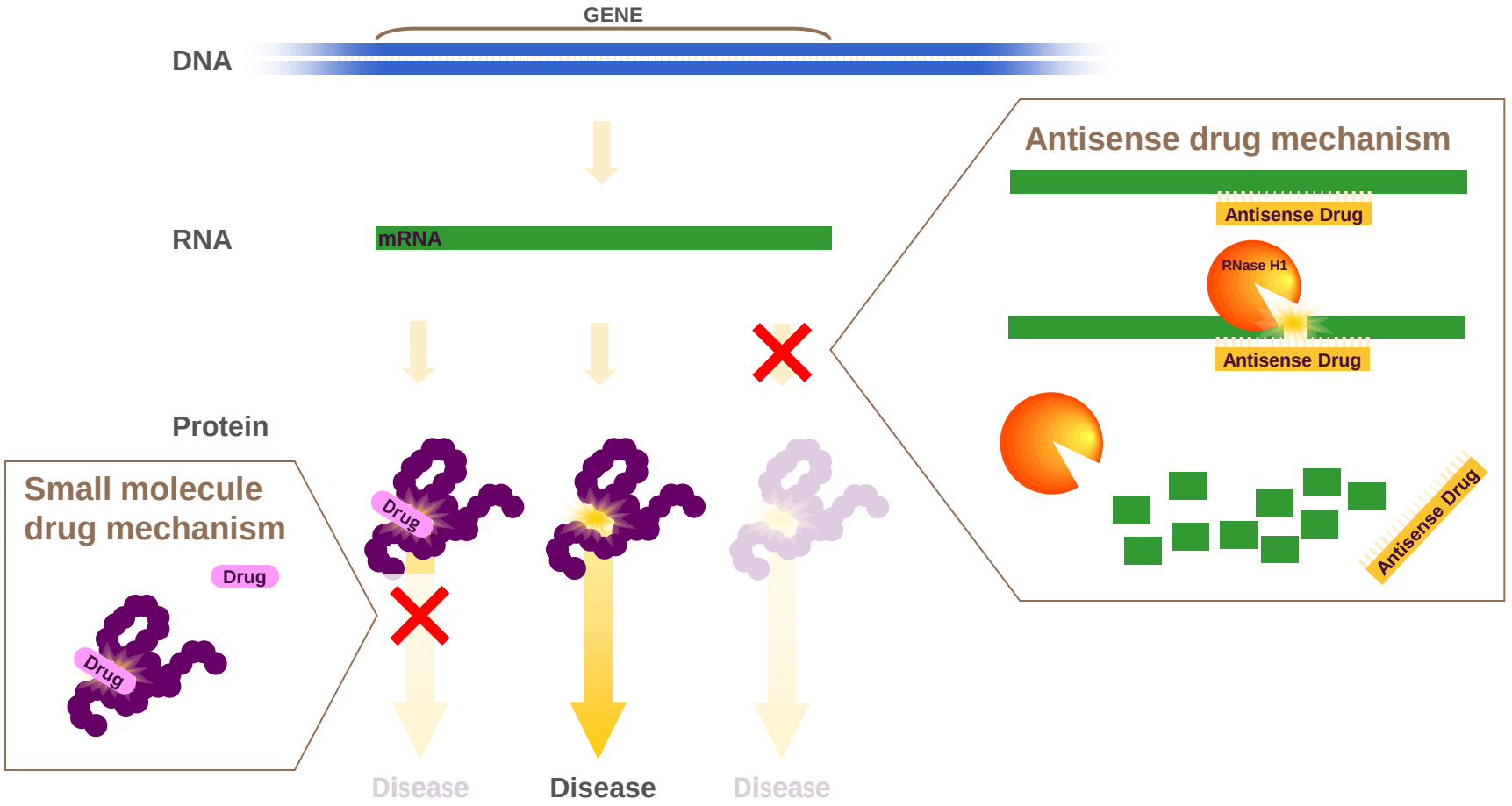
Isis Today

- **KYNAMRO™: First Systemically Delivered Antisense Drug Approved in the US**
  - FOCUS FH phase III study to support label expansion in the US and possible EU approval
- **Constantly Maturing Pipeline**
  - Nine drugs with Phase 2 or Phase 3 data expected in 2013/early 2014
  - Two to three Phase 3 programs initiating in 2013/early 2014
  - Five drugs with launch potential by 2017/2018
- **Expanding Portfolio of Drugs and Therapeutic Areas**
  - Four new drugs in development over the last 12 months for a total of 28
  - Growing severe, rare and orphan disease program
- **Leader in Antisense Technology**
  - Continued improvements in the potency and side effect profile
  - Over 1,500 patents protecting the portfolio
- **Partnerships Validating the Platform, Complementing Isis' Expertise and Ensuring Financial Strength**
  - Five new collaborations in the last year and a half, three in the last six months alone, bringing in $126mm in upfront payments and over $2.5bn in total potential value (AstraZeneca, Biogen Idec and Roche)

Leaders in Antisense

A traditional small molecule drug inhibits a disease-causing protein based on the shape of the protein

An antisense drug inhibits the production of a disease-causing protein based on the protein's mRNA and gene sequence



Isis' Clinical-Stage Pipeline

Therapeutic Area	Indication	Partners	Drugs	Phase I	Phase II	Phase III	Reg & Comm
Cardiovascular	Severe HeFH	genzyme A SANOFI COMPANY	KYNAMRO™				
	CAD		ISIS-APOCIII$_{RX}$				
	CAD		ISIS-CRP$_{RX}$				
	Clotting Disorders		ISIS-FXI$_{RX}$				
	CAD		ISIS-APOA$_{RX}$				
Severe & Rare	Homozygous FH	genzyme A SANOFI COMPANY	KYNAMRO™				
	Pouchitis	Atlantic	Alicaforsen				*Named Patient Supply
	TTR Amyloidosis	gsk	ISIS-TTR$_{RX}$				
	Spinal Muscular Atrophy	biogen idec	ISIS-SMN$_{RX}$				
	Severe HTG		ISIS-APOCIII$_{RX}$				
	Acromegaly	antisense	ATL1103				
	Cushing's Syndrome		ISIS-GCCR$_{RX}$				
Metabolic	Diabetes		ISIS-PTP1B$_{RX}$				
	Diabetes		ISIS-GCCR$_{RX}$				
	Diabetes		ISIS-GCGR$_{RX}$				
	Obesity		ISIS-FGFR4$_{RX}$				
Cancer	Cancer	TEVA OncoGenex	Custirsen				
	Cancer		ISIS-EIF4E$_{RX}$				
	Cancer	OncoGenex	OGX-427				
	Cancer	AstraZeneca	ISIS-STAT3$_{RX}$				
Inflammation	Inflammation		ISIS-CRP$_{RX}$				
& Other	MS	antisense	ATL1102				
	Local Fibrosis	EXCALIARD Pfizer	EX0 001				
	Ocular Disease	iCo Therapeutics Inc.	iCo-007				
	Severe Bacterial Infection	ACHAOGEN	Plazomicin				

Isis' Pre-clinical Stage Pipeline

April 2013

Therapeutic Area	Indication	Partners	Drugs	Preclinical	Phase I	Phase II	Phase III	Reg & Comm
Cardiovascular	Clotting Disorders		ISIS-FVII$_{Rx}$					
Severe & Rare	AAT Liver Disease	gsk	ISIS-AAT$_{Rx}$					
	Hereditary Angioedema		ISIS-PKK$_{Rx}$					
Metabolic	NASH		ISIS-DGAT2$_{Rx}$					
Cancer	Cancer	AstraZeneca	ISIS-AZ1$_{Rx}$					
Inflammation	Anemia of Inflammation	XENON	XEN701					
& Other	Antiviral	gsk	ISIS-GSK3$_{Rx}$					

Potential Drug Launches Through 2018

Drug	Indication/Market	Economics
ISIS-TTR$_{Rx}$ 	Familial Amyloid Polyneuropathy (FAP) ~10,000 patients	License fee, sales milestone payments and double-digit royalties
ISIS-SMN$_{Rx}$ 	Spinal muscular atrophy (SMA) ~35,000 patients worldwide	License fee, milestone payments and double-digit royalties
ISIS-APOCIII$_{Rx}$ 	Severe triglyceridemia (>880 mg/dL) at increased risk of recurrent pancreatitis ~200,000 patients in US & EU	Isis Owned
Custirsen (OGX-011) 	Castration-resistant prostate cancer (1st line) ~315,000 patients in US/EU	Milestone payments and single-digit royalties
EXC 001 	Anti-scarring treatment estimated to be multibillion dollar market	Milestone and other payments and single-digit royalties

KYNAMRO's Approval Has Validated Our Platform

First Systemic Antisense Drug on the Market

KYNAMRO mipomersen sodium genzyme A SANOFI COMPANY

- **KYNAMRO approved by FDA for homozygous FH on January 29, 2013**
  - $25M milestone earned
- **Commercial activities underway via Genzyme / Sanofi**
  - Physicians qualified, scripts written and reimbursement obtained
  - Focus on improving disease awareness and treatment of homozygous FH patients
- **Investing in the future – FOCUS FH Phase III study in severe FH patients ongoing (under SPA)**
  - Projected completion by year end 2014

Evolving Business Strategy

1989	2013	Future
■ Limited financial flexibility	■ Increased financial flexibility	■ Commercial revenues and greater financial flexibility
■ Partner controls development	■ Isis controls early and mid-stage development	■ ISIS controls early and possibly later stage development
■ Research programs funding technology and pipeline development ■ Research / early stage partnerships	■ Transactions, reflecting ISIS continuing investment in partnered programs ■ Preferred partner / option transactions	■ Transaction structures reflect greater Isis investment and control of drugs ■ Late stage preferred partner / option transactions

Criteria for Partnering

Partner Early	License After POC	Keep Longer
■ Complex, difficult and/or expensive development path	■ Complex development path	■ Clear development path
■ Expertise from partner could provide increased likelihood of success	■ High development cost	■ Low to moderate development costs
■ Significant technical risk (i.e., new route of administration, new mechanism)	■ Outcome studies required or likely	■ Potential for rapid route to market in small indication, followed by expansion into larger indications
	■ No recognized approvable endpoints	■ Diseases in which antisense technology has a clear advantage
	■ Large patient population	■ Therapeutic areas and clinical studies in which Isis has prior knowledge and expertise to leverage
	■ Large marketing and sales effort	
	■ Broad group of treating physicians	

Examples:

ISIS-SMN$_{Rx}$	**ISIS-CRP$_{Rx}$**	**ISIS-APOCIII$_{Rx}$**
ISIS-STAT3$_{Rx}$	**ISIS-FXI$_{Rx}$**	**ISIS-PKK$_{Rx}$**
		ISIS-APOA$_{Rx}$

biogen idec

AstraZeneca

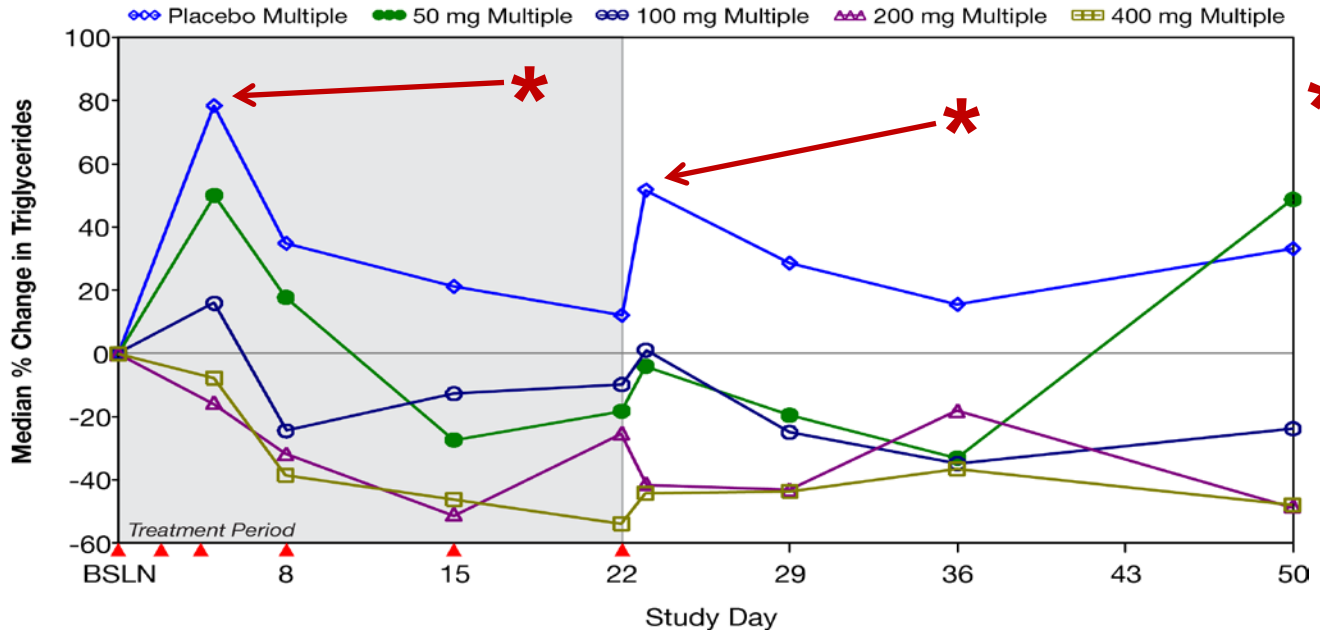
ISIS-APOCIII$_{Rx}$ for Severe Hypertriglyceridemia

An Isis-Owned Rare Disease Opportunity

- **More than 200K patients in US and EU with severe hypertriglyceridemia (HTG) (triglycerides of >880 mg/dL)**
  - Significant risk of developing recurring pancreatitis, often requiring multiple hospitalizations and may require surgery
  - High risk for cardiovascular disease
  - Frequently occurs in patients with type 2 diabetes
- **Standard therapies, including niacin, fibrates and fish oil are inadequate**
- **Potential for broader utility in cardiovascular disease and metabolic syndrome, including diabetes**

ISIS-APOCIII$_{Rx}$ Phase I in Healthy Volunteers

Dose-Dependent Reduction in Fasting and Diet-Induced Triglycerides



* Fasting TGs increase due to high-fat diet

Safety Summary

- No SAEs, no clinically significant increases in liver enzymes or other lab chemistries
- No flu-like symptoms and very low incidence of mild injection site reactions

ISIS-APOCIII$_{Rx}$ Ongoing Studies

Ongoing Studies

Phase 2 in Patients with Severe or Uncontrolled Hypertriglyceridemia

- **Multicenter randomized double-blind placebo controlled study**
- **Study designed to demonstrate that ISIS-APOCIII$_{Rx}$ can decrease triglycerides and ApoC-III in patients with severely elevated triglycerides (TG), alone and in combination with fibrates**
  - Patients not on TG-lowering therapy with fasting TG levels ≥500 & ≤2000 mg/dL
    - 72 patients / 100, 200 & 300 mg 13 weeks / 3:1 (active:placebo)
  - Patients on stable dose fibrates with fasting TG levels ≥225 & ≤2000 mg/dL
    - 24 patients / 200 & 300 mg 13 weeks / 2:1 (active:placebo)
- **Also will evaluate effects of ISIS-APOCIII$_{Rx}$ on fasting & post-prandial TG levels**
- **Data planned for <u>mid 2013</u>**

Phase 2 Study in T2DM Patients with Elevated Triglycerides

- **Randomized double-blind placebo controlled study**
- **Study designed to demonstrate that ISIS-APOCIII$_{Rx}$ can decrease triglycerides and ApoC-III in type II diabetes patients with moderately elevated triglycerides**
  - ~24 patients diagnosed with T2DM ≥6 months on stable dose metformin ≥ 1mg at least 4 weeks (HbA1C ≥7.0% - <9.0% and fasting TG levels ≥200 & ≤500 mg/dL)
  - Randomized 2:1 to receive 300 mg ISIS-APOCIII$_{Rx}$ or placebo
- **Also will evaluate effects of ISIS-APOCIII$_{Rx}$ on whole body insulin sensitivity, diabetic profile & lipid profile, including fasting & post-prandial TG levels**
- **Data planned for <u>late 2013</u>**

ISIS-APOCIII$_{Rx}$

Rapid Path to Market

- **Phase 3 study in patients with severe hypertriglyceridemia (TG > 880 mg/dL)**
  - Planned to begin in early 2014
  - US & EU regulatory meetings planned for 2013
- **Data planned for late 2015**
- **Potential regulatory filing in 2016**
- **Potential commercial launch in 2016/2017**
- **Isis owned program**

Partnered with: biogen idec

ISIS-SMN$_{Rx}$ for Spinal Muscular Atrophy (SMA)

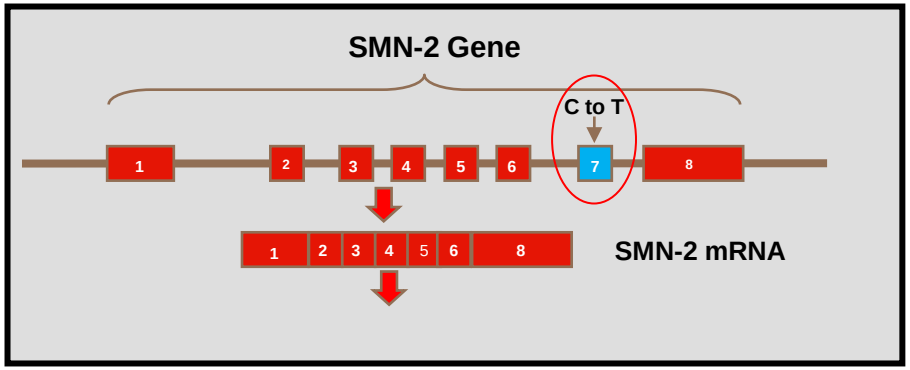
Severe Genetic Neuromuscular Disease Affecting Children

- **SMA is a rare disease that affects approximately 30-35K children in United States, Europe and Japan**
  - Number one genetic cause of death in infants
  - Characterized by progressive muscle atrophy and loss of motor function
- **Caused by genetic defects in the SMN1 gene that result in the lack of functional SMN protein**
- **No currently approved therapies for SMA**

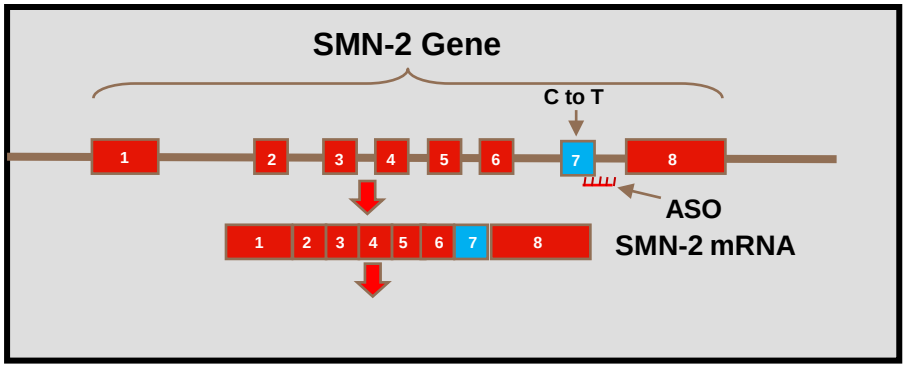
ISIS-SMN$_{Rx}$

Modulating RNA Processing to Positively Impact Disease

- A related gene, SMN2, normally produces only a small amount of functional SMN protein because of inappropriate RNA processing
- ISIS-SMN$_{Rx}$ increases the production of functional SMN protein by promoting appropriate RNA processing



SMN2 gene does not normally produce enough SMN protein to compensate for loss of SMN1 gene in patients with SMA. Splicing mechanism removes exon 7 resulting in a shortened defective SMN protein



ISIS-SMN$_{Rx}$ keeps exon 7 in the RNA and leads to the production of functional SMN protein

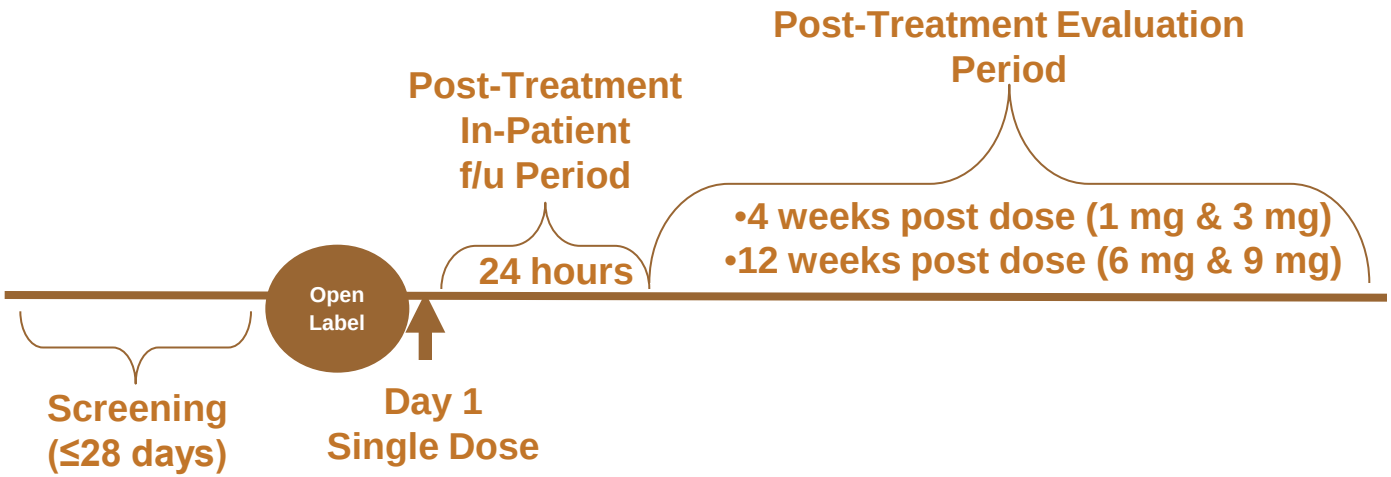
Partnered with: biogen idec

ISIS-SMN$_{Rx}$

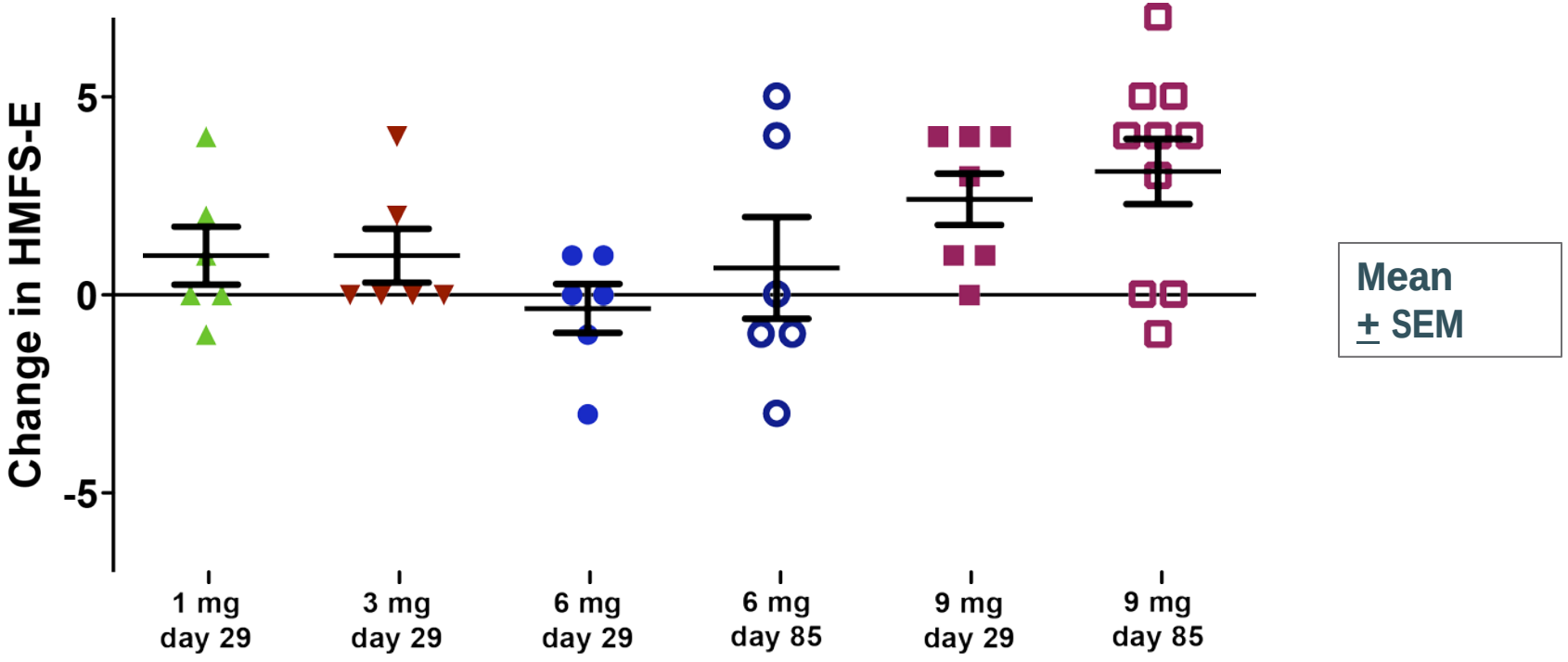
Phase I Single-Dose Study in SMA Patients (Completed)

- **Open-label, single-dose study to evaluate the safety and tolerability of ISIS-SMN$_{Rx}$ in SMA patients 2-14 years of age**
  - Intrathecal dosing was well tolerated
  - Feasibility of infrequent dosing demonstrated
  - Improvements in Hammersmith scores, a measure of muscle function, were observed in a number of children

Cohorts	n
1 mg	6
3 mg	6
6 mg	6
9 mg	10



Exploratory Outcome Measure
Hammersmith Motor Function Scale – Expanded



- **In the 9 mg dose group at Day 85**
  - Mean change from baseline = 3.1 points (p=0.02); % change = 17.6%
  - 6/10 subjects with change ≥4 points (3/6 were ≥5 years old)

Partnered with:

biogen idec

ISIS-SMN$_{Rx}$ – Ongoing Studies

Phase 1b/2a Multiple-Dose Study in SMA Patients (Ongoing)

- **Open-label, intrathecal, dose escalation study in SMA patients 2-15 years of age**
- **Objectives**
  - Determine dose and dose interval for Phase 3 study
  - Evaluate the safety and tolerability of multiple doses of ISIS-SMN$_{Rx}$
  - Evaluate biomarkers and clinical outcomes related to SMA
  - Determine appropriate Phase 3 endpoints
- **Data planned for late 2013/early 2014**

Phase 2 Infantile-onset Study (Initiated)

- **Open-label, intrathecal, multiple dose study in eight infants with SMA**
- **Objectives**
  - Determine dose and dose interval for Phase 3 study
  - Evaluate the safety and tolerability of multiple doses of ISIS-SMN$_{Rx}$ in patients between the ages of three weeks and seven months
  - Evaluate biomarkers and clinical outcomes related to SMA
- **Data planned for late 2013/early 2014**

Partnered with:

biogen idec®

ISIS-SMN$_{Rx}$

Rapid Path to Market

- **Granted Orphan Drug Status in US and EU and Fast Track Designation in US**
- **Two pivotal programs planned to start in 2013/early 2014**
  - Infant onset Phase 2/3 studies (~50 patients)
  - Childhood onset Phase 3 study (~120 patients)
- **Potential filing in 2016-2017 followed by launch in 2017-2018**
- **Attractive economics**
  - $74M in upfront payment and pre-licensing milestones
  - $225M in license fee and post-licensing milestone payments
  - Double-digit royalties

Splicing Disorders

A Novel Area for Antisense Drugs

- **ISIS-SMN$_{RX}$ is the first drug designed to treat splicing disorders**
- **Other splicing diseases that could be addressed with antisense drugs**
  - Duchenne muscular dystrophy
  - Thalassemia
  - Progeria
  - Neurofibromatosis type 1
  - Cystic fibrosis
  - Pheochromocytoma
  - Long QT syndrome
  - Familial dementia

Examples of Other Programs Isis Intends to Keep Longer

Well Defined Clinical Path and Efficient Path to Market

- **ISIS-PKK$_{Rx}$ for Hereditary Angioedema**
  - HAE is a rare genetic disease characterized by rapid, painful and potentially fatal attacks of severe edema, which are caused by an inflammatory response
  - Approximately 15-20K patients in US and EU
  - Current prophylactic treatments (androgens) are either inadequate or very difficult to use
  - Unmet need: Up to 80% of patients are not using IV prophylaxis and could use a s.c. prophylactic if effective and available
  - Development path relatively straightforward and potentially rapid

- **ISIS-APOA$_{Rx}$ for patients with severely elevated Lp(a)**
  - Lp(a) is an independent risk factor for coronary heart disease and stroke
  - Approximately 160K patients in US and EU have severely elevated Lp(a) ≥250 mg/dL
  - Most commonly prescribed lipid-reducing drugs have little or no effect on Lp(a) concentration
  - Potentially rapid development path in severe patient population

Advancing Antisense Technology

New Mechanisms, New Routes of Delivery, Better Performance

- **New Mechanisms**
  - RNA Processing/Splicing
  - Single-stranded RNAi
- **New Routes of Delivery**
  - Intrathecal
  - Intradermal
- **Better Performance**
  - Improved screening produces more potent and better tolerated 2nd Generation antisense drugs
  - Generation 2.5 antisense drugs even more potent

Recent Partnering Transactions Validating the Platform and Illustrating Future Potential for Isis

Date	Partner	Focus / Products	Upfront	Total Value
Jan-2012	biogen idec	Spinal Muscular Atrophy	$29mm	~$300mm
Jun-2012	biogen idec	Myotonic Dystrophy	$12mm	~$270mm
Dec-2012	biogen idec	Neurological Disorders	$30mm	>$660mm
Dec-2012	AstraZeneca	ISIS-STAT3$_{RX}$ and Oncology	$25mm	~$1bn
Apr-2013	Roche	Huntington's Disease	$30mm	~$360mm

Advancing the Pipeline

Multiple Data Read Outs and Value Creation Opportunities in 2013 / Early 2014

Drug	Studies (Indication)	Partner	Data Timing
ISIS-CRP$_{Rx}$	Phase 1 – Endotoxin study Phase 2 - RA (Inflammation) Phase 2 - Atrial Fibrillation (Cardiovascular Disease)	**Isis Owned**	Q1 2013 ✓ Mid 2013 2014
ISIS-APOCIII$_{Rx}$	Phase 2 - Severe Hypertriglyceridemia (HTG) Phase 2 - Type 2 Diabetes with Moderate HTG	**Isis Owned**	Mid 2013 Late 2013
ISIS-EIF4E$_{Rx}$	Phase 2 - Lung Cancer Phase 2 - Prostate Cancer	**Isis Owned**	2013
OGX-427	Phase 2 - Prostate Cancer	Oncogenex	2013
ISIS-STAT3$_{Rx}$	Phase 2 - Lymphoma	AstraZeneca	Late 2013/Early 2014
ISIS-SMN$_{Rx}$	Phase 1 – Spinal Muscular Atrophy Phase 2 - Spinal Muscular Atrophy (infantile onset) Phase 2 - Spinal Muscular Atrophy (childhood onset)	Biogen	Q1 2013 ✓ Late 2013/Early 2014 Late 2013/Early 2014
iCo-007	Phase 2 - Diabetic Macular Edema	iCo Therapeutics	Early 2014
OGX-011	Phase 3 - Prostate Cancer	Oncogenex	1H 2014
ISIS-FXI$_{Rx}$	Phase 2 - Total Knee Replacement (Thrombosis)	**Isis Owned**	2014

Multiple Investment Opportunities across the Pipeline

Drugs with Phase II and III Studies Planned for 2013 / Early 2014

Drug	Studies (Indication)	Partner	Initiation Timing
ISIS-TTR$_{Rx}$	Phase 2/3 (Familial Amyloid Polyneuropathy [FAP])	GSK	Q1 2013 ✓
ISIS-SMN$_{Rx}$	Phase 2 (Spinal Muscular Atrophy – infantile onset) Phase 3 (SMA – infantile onset) Phase 3 (SMA – childhood onset)	Biogen	Q1 2013 ✓ Early 2014 Early 2014
OGX-427	Phase 2 (Lung Cancer) Phase 2 (Pancreatic Cancer)	Oncogenex	Mid 2013 2013
ISIS-STAT3$_{Rx}$	Phase 2 (Cancer)	AstraZeneca	Q2 2013 ✓
ISIS-PTP1B$_{Rx}$	Phase 2 (Type 2 Diabetes)	**Isis Owned**	2013
ISIS-GCGR$_{Rx}$	Phase 2 (Type 2 Diabetes)	**Isis Owned**	2013
ISIS-GCCR$_{Rx}$	Phase 2 (Type 2 Diabetes) Phase 2 (Cushing's Syndrome)	**Isis Owned**	2013 2014
ISIS-APOCIII$_{Rx}$	Phase 3 (Severe Hypertriglyceridemia)	**Isis Owned**	Early 2014

Key Management

Stanley T Crooke, M.D., Ph.D.
Chairman of the Board & CEO
(24 years at Isis)

B Lynne Parshall, Esq.
Director & COO
(22 years at Isis)

C Frank Bennett, Ph.D.
Sr. VP Research
(24 years at Isis)

Richard S Geary, Ph.D.
Sr. VP Development
(17 years at Isis)

Brett P. Monia, Ph.D.
Sr. VP Antisense
Drug Discovery
(24 years at Isis)

Beth Hougen
Sr. VP of Finance & CFO
(13 years at Isis)

Patrick O'Neil, Esq.
Sr. VP of Legal
& General Counsel
(12 years at Isis)

Isis Financial Position

March 31, 2013 (in millions)

	3 Months Ended, March 31	
	2013	2012
Revenue	$ 43	$ 23
Operating Expenses – Pro forma [1]	39	39
Loss from Operations – Pro forma [1]	4	(16)
Net Income (Loss) – Pro forma [1]	1	(22)

	At March 31, 2013
Cash & Short-term Investments [2]	$ 372
2¾% Convertible Notes [3]	201
Deferred Revenue (Long-term Portion)	59
Long-term Financing Liability for Leased Facility [4]	71
Stockholders' Equity	201

[1] Amounts exclude non-cash compensation expense related to equity awards.

[2] This amount does not include the $30M we received in April 2013 from our recently announced Roche transaction.

[3] Amount represents the principal balance of the Notes. On the balance sheet, the carrying value of the Notes is $146 million due to the adoption of FSP 14-1.

[4] Accounting rules required Isis to record the cost of its leased facility as a fixed asset with a corresponding liability.

Isis – Opportunity to Invest in Leading Antisense Pipeline and Platform

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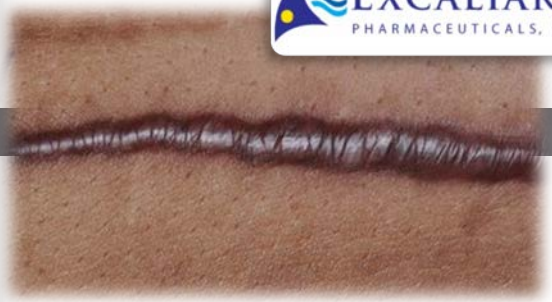
genzyme

Pfizer

EXCALIARD
PHARMACEUTICALS, INC.



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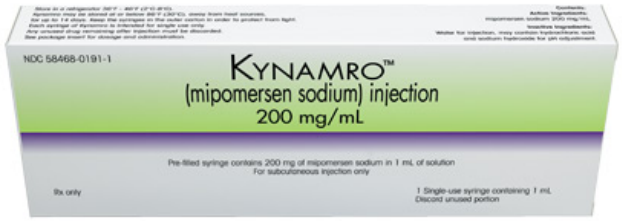
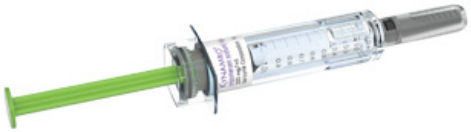
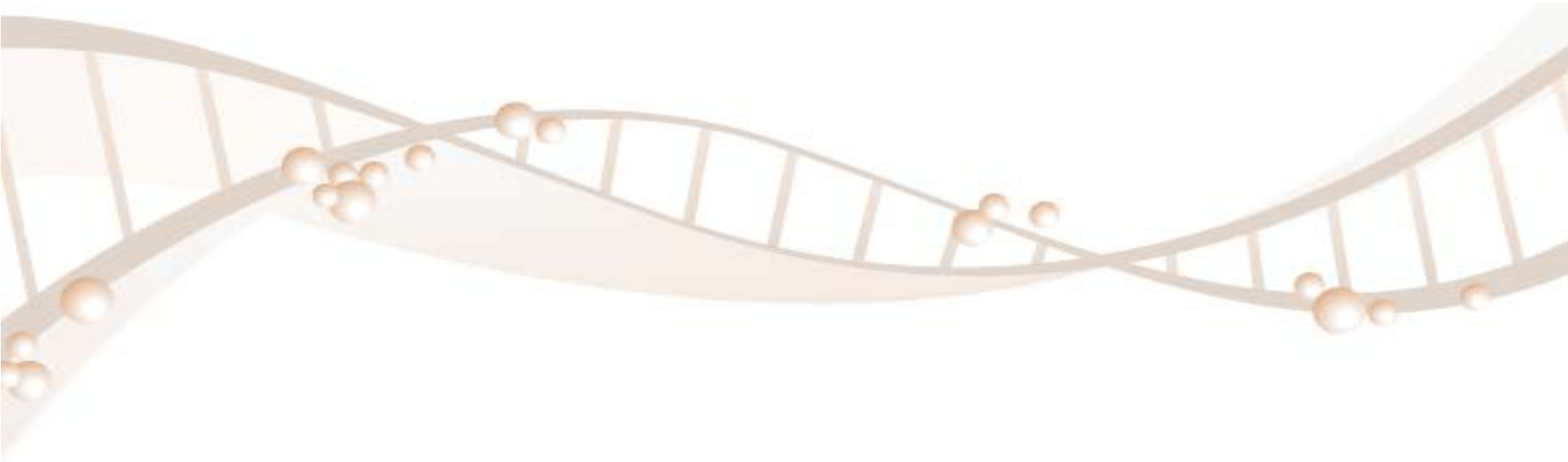




biogen idec®

Appendix



Advantages of our Antisense Technology Platform

Direct Route from Genes to Drugs	***Uniquely specific & broadly applicable***
Efficient Discovery & Early Development	***Dramatically reduced cost & increased success in R&D***
Investment Amortized Across the Entire Pipeline	***Chemistry, manufacturing, formulation, analytical methods***
Generate an Evergreen Pipeline	***Robust, diversified pipeline adding 3-5 new drugs per year***